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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/574,460	05/18/2000	Michael A. Apicella	17023.004US1	6817

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EXAMINER

PAK, YONG D

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/574,460	Applicant(s) APICELLA ET AL.	
	Examiner Yong D. Pak	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 30-50 and 52-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 30-50 and 52-58 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The final amendment filed on August 22, 2006, amending claims 39 and 48, canceling claim 51 and adding claims 56-58, has been entered.

Claims 30-50 and 52-58 are pending and are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on August 22, 2006, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 and claims 31-38 depending therefrom rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 recites the phrase "Haemophilus influenzae-specific lipooligosaccharide (LOS)". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner what is considered as "Haemophilus influenzae-specific" by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition, those

skilled in the art would be unable to conclude if a LOS is indeed a "*Haemophilus influenzae*-specific" LOS without knowing the metes and bounds of the phrase.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that one of ordinary skill in the art would know that the phrase refers to the *H. influenzae*-specific LOS that is synthesized by the addition of an acceptor molecule to the terminal heptose molecule and that one skilled in the art can determine whether the LOS is a *H. influenzae*-specific by determining whether the LOS is recognized by monoclonal antibody 6E4. Examiner respectfully disagrees. The specification teaches that only the core of *H. influenzae* LOS is associated with a 6E4 epitope. However, the instant claims are drawn to producing LOS by attaching acceptor molecules to the terminal heptose of a core structure of any gram-negative bacteria, which may or may not have a 6E4 epitope. Therefore, one having ordinary skill in the art would be unable to conclude if a LOS is indeed a "*Haemophilus influenzae*-specific" LOS.

Hence the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-50 and 52-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 30-50 and 52-58 are drawn to a method of producing a *H. influenzae* specific lipooligosaccharide (LOS) or complex carbohydrate by culturing a gram-negative bacteria comprising a polynucleotide encoding an undecaprenyl-phosphate N-acetyl glucosaminyl phosphate transferase (rfe), wherein said bacteria is transformed with a polynucleotide encoding a lipooligosaccharide-synthesis gene G polypeptide (lsgG) from *H. influenzae*, wherein a terminal heptose of a lipopolysaccharide (LPS) or LOS core structure of said gram-negative bacterial species is modified by the addition of N-acetyl glucosamine. The claims encompass a method of producing any or all *H. influenzae* specific LOS by transforming any or all Gram-negative bacteria, *E. coli* or *S. minnesota* with any or all polynucleotides encoding a LsgG from *H. influenzae*, including any or all variants, mutants and recombinants thereof, wherein said Gram-negative bacteria, *E. coli* or *S. minnesota* endogenously comprises any or all polynucleotides encoding a rfe from any source or are transformed with any or all polynucleotides encoding a rfe from *H. influenzae*, including any or all variants, mutants and recombinants thereof. Therefore, the claims are drawn to a method of producing *H. influenzae* specific LOS using a (A) genus comprising any or all Gram-negative bacteria, *E. coli* or *S. minnesota*, wherein said bacteria is transformed with (B) a genus comprising any or all polynucleotides encoding a LsgG from *H. influenzae*, having any structure and (C) is transformed with a genus of any or all polynucleotides encoding a

rfe from any source or *H. influenzae* having any structure if said bacteria endogenously does not produce rfe.

The specification only describes a method of producing specific LOS described in Table 2 and 3 by transforming *E. coli* with a polynucleotide encoding lsgG isolated from *H. influenzae* (pGEMLOS-4, pGEMLOS-5 or PGEMLOS-7), wherein the polynucleotide encoding rfe is endogenous to the *E. coli*. This one example is not enough and does not constitute a representative number of species to describe the whole genus comprising any or all LOS, genus comprising any or all Gram-negative bacteria, genus comprising any or all polynucleotides encoding rfe or genus comprising any or all polynucleotides encoding lsgG. There is no evidence on the record of the relationship between the structure of the polynucleotide encoding lsgG in pGEMLOS-4 and the structure of any or all polynucleotides encoding lsgG, including any or all recombinants, mutants and variants thereof. Similarly, there is no evidence on the record of the relationship between the structure of the polynucleotide encoding rfe endogenous to *E. coli* and the structure of any or all polynucleotide encoding rfe, including any or all recombinants, mutants and variants thereof. There is also no evidence on the record of a method for successfully producing any or all LOS in any or all Gram-negative bacteria. Therefore, the specification fails to describe a representative species of the genus comprising any or all polynucleotides encoding rfe and genus comprising any or all polynucleotides encoding lsgG and used to transform a genus comprising any or all Gram-negative bacteria to produce any or all *H. influenzae* specific LOS.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 30-50 and 52-58.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the structural characteristics of the bacteria and DNA sequences recited in the claims are provided since the claims recite that the gram-negative bacteria used in the method comprise a DNA sequence encoding *rfe* endogenous to the bacterium or any of the *rfe* genes available in the art. Examiner respectfully disagrees. In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics,

i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In the instant case, the recitation of "rfe" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "rfe" genes, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from

other proteins such that one can visualize or recognize the identity of the members of the genus.

Applicants also argue since the claims recite using a DNA sequence encoding a LsgG from *H. influenzae*, which is available in public databases, the claims are fully described. Examiner respectfully disagrees. The claims are drawn to a method of using a genus comprising any or all polynucleotides encoding a LsgG from *H. influenzae*, having any structure, since the claims are not limited to only the wild type sequence, but any or all variants, mutants and recombinants of a LsgG from *H. influenzae*. As discussed above, since there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In the instant case, the recitation of "LsgG from *H. influenzae*" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. There is also no evidence on the record of the relationship between the structure of the polynucleotide encoding lsgG in pGEMLOS-4 and the structure of any or all polynucleotides encoding lsgG, including any or all recombinants, mutants and variants thereof.

Applicants also argue that the specification demonstrate the feasibility of using *Salmonella minnesota* to make complex carbohydrates with the *lsg* locus and that skilled artisan was well apprised of gram-negative bacteria other than *E. coli* and *S. minnesota* that could be used in the claimed methods. Examiner respectfully disagrees.

There is also no evidence on the record of a method for successfully producing any or all LOS in any or all Gram-negative bacteria, other than *S. minnesota* and *E. coli*.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30-32, 34, 36-41, 43, 45-47, 49-50 and 56-55 are rejected under 35 U.S.C. 102(b) as being anticipated by McLaughlin et al.

Claims 30-32, 34, 36-41, 43, 45-47, 49-50 and 56-55 are drawn to a method of producing LOS or complex carbohydrate and a method of adding a N-acetyl glucosamine to a terminal heptose of a LOS or LPS core structure using an *E. coli* K-12 strain JM109, transformed with a polynucleotide encoding a lsgG from *H. influenzae*, wherein a polynucleotide encoding rfe is part of said *E. coli*'s genome and said rfe is regulated by said LsgG.

McLaughlin et al. (form PTO-1449) discloses to a method of producing *H. influenzae* specific LOS, a complex carbohydrate, using an *E. coli* K-12 strain JM109 transformed with a polynucleotide encoding a lsgG from *H. influenzae*, wherein said *E.*

coli endogenously comprises a polynucleotide encoding a *rfe* polynucleotide (pages 165-166). The LOS produced is *H. influenzae* specific since it is recognized by antibodies raised against *H. influenzae* LOS (pages 166, 170 and 172). In the method of McLaughlin et al., N-acetyl glucosamine is added to a terminal heptose of a LOS or LPS core structure. The *E. coli* of McLaughlin et al. inherently possesses a polynucleotide encoding *rfe* since *E. coli* endogenously produces *rfe* (See Alexander et al. – form PTO-1449) and the claims do not recite transforming *E. coli* with *rfe*. Regulation of *rfe* by LsgG is an inherent property of LsgG, which would flow naturally when both polynucleotides are present. Therefore, the reference of McLaughlin et al. anticipates claims 30-32, 34, 36-41, 43, 45-47, 49-50 and 56-55.

Since the Office does not have facilities for examining and comparing applicant's *E. coli* and the *E. coli* of McLaughlin et al. used in the method of McLaughlin et al., the burden is on the applicant to show a novel or unobvious difference between the product used in the claimed method and the product used in the prior art (i.e., that the *E. coli* transformant of the prior art does not possess the same material structure and functional characteristics of the claimed *E. coli* transformant). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that the reference of McLaughlin et al. does not anticipate the instant claims because McLaughlin et al. relates to the DNA sequence analysis of the

lsg cluster and to the analysis of proteins encoded by the lsg cluster, whereas the instant claims recite the step of recovering *H. influenzae*-specific LOS or complex carbohydrate from the culture medium. Examiner respectfully disagrees. McLaughlin et al. does disclose a step of recovering *H. influenzae*-specific LOS or complex carbohydrate from the culture medium; LOS was "recovered" by digestion of cells with a proteinase to isolate LOS using a method detailed in McLaughlin et al. (J Bacteriol. 1992 Oct;174(20):6455-9 – form PTO-892), see page 6456 "LOS isolation".

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 33, 35, 42, 44, 48 and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLaughlin et al. in view of Preston et al. and Swierzko et al.

Claims 33, 35, 42, 44, 48 and 52-55 are drawn to a method of producing LOS or complex carbohydrate and a method of adding a N-acetyl glucosamine to a terminal heptose of a LOS or LPS core structure using a *S. minnesota* transformed with a polynucleotide encoding a rfe from *H. influenzae* and a polynucleotide encoding a LsgG from *H. influenzae*.

McLaughlin et al. discloses a method of producing LOS or complex carbohydrate using an *E. coli* K-12 strain JM109 which comprises a polynucleotide encoding a *rfe* and wherein said *E. coli* is transformed with a polynucleotide encoding a *LsgG* from *H. influenzae*, as discussed above.

The reference of McLaughlin et al. does not teach a method of transforming a *S. minnesota* with a polynucleotide encoding a *rfe* from *H. influenzae*.

Preston et al. (from PTO-1449) discloses several genes involved in LOS biosynthesis, including the *lsg* gene and *rfe* gene isolated from *H. influenzae* (Table page 154). Preston et al. teaches that *H. influenzae* produce LOS lacking O-antigens, which are present in LPS produced by most Gram-negative bacteria. Alexander et al. (from PTO-1449) confirms said teaching by disclosing that the *rfe* gene isolated from *E. coli* is involved in O-antigen synthesis of LPS (page 7079, abstract).

Swierzko et al. (cited previously on form PTO-892) discloses that *S. minnesota* bears a terminal heptose molecule and discloses using this bacterium as a transformant in synthesizing LPS (pages 3216-3217). *S. minnesota* is an useful host due to their rapid growth in the laboratory (page 3216) and produces LPS.

Therefore, in combining the teachings of Preston et al., McLaughlin et al. and Swierzko et al, it would have been obvious to one having ordinary skill in the art modify the method of McLaughlin et al. by transforming *E. coli* or *S. minnesota* et al. with the *rfe* gene of Preston et al. in addition to the *lsg* gene. One of ordinary skill in the art would have been motivated to use the *rfe* gene of Preston et al. in gram-negative

bacterium producing LPS with O-antigens, such as *E. coli* and *S. minnesota*, in order to produce *H. influenzae* specific LOS, which lack O-antigens in their structure. One of ordinary skill in the art would have had a reasonable expectation of success since Preston et al. teaches a *rfe* gene and Swierzko et al. teaches using *S. minnesota* as an effective transformant.

Therefore, the above references render claims 33, 35, 42, 44, 48 and 52-55 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that the claims are not obvious because McLaughlin et al. does not teach a method of transforming *S. minnesota* with a polynucleotide encoding a *rfe* from *H. influenzae* or steps of recovering *H. influenzae*-specific LOS or complex carbohydrate from the culture medium, but relates to the DNA sequence analysis of the *lsg* cluster and to the analysis of proteins encoded by the *lsg* cluster. Examiner respectfully disagrees. As discussed above, McLaughlin et al. does disclose a step of recovering *H. influenzae*-specific LOS or complex carbohydrate from the culture medium; LOS was "recovered" by digestion of cells with a proteinase to isolate LOS using a method detailed in McLaughlin et al. (J Bacteriol. 1992 Oct;174(20):6455-9 – form PTO-892), see page 6456 "LOS isolation". Regarding transformation of *S. minnesota* and *rfe* gene, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the reference of McLaughlin et al. is relied upon for its disclosure of a method of producing LOS or complex carbohydrate using a polynucleotide encoding a rfe that is endogenous to *E. coli* and a polynucleotide encoding a LsgG from *H. influenzae*. Swierzko et al. is relied upon for its disclosure of transformation of *S. minnesota* and Preston et al. is relied upon for its disclosure of a *H. influenzae* rfe.

Applicants also argue that the claims are not obvious because rfe is involved in the biosynthesis of enterobacterial common antigen (ECA), the biosynthesis of the O7 repeat of *E. coli* as well as other O-specific polysaccharides (by referencing to Alexander et al) and LOS molecules are not the same as ECA, O7 repeats or other O-specific polysaccharides. The rejection does not presume that LOS molecules are the same as ECA, O7 repeats or other O-specification polysaccharides. Further, Alexander et al. discloses that rfe isolated from *E. coli* is involved in biosynthesis of enterobacterial common antigen (ECA), the biosynthesis of the O7 repeat of *E. coli* as well as other O-specific polysaccharides. The motivation of using rfe isolated from *H. influenzae* of Preston et al. is to produce *H. influenzae*-specific complex carbohydrate or LOS which lack O-antigens in *E. coli* and *S. minnesota*, both bacteria which normally produce LPS with O-antigens.

Applicants also argue that the references do not disclose rfe regulation by LsgG. Regulation of rfe by LsgG is an inherent property of LsgG, which would flow naturally when both polynucleotides are present.

Hence the rejection is maintained.

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Application/Control Number:
09/574,460
Art Unit: 1652

Page 16

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

A handwritten signature in black ink, appearing to read 'Manjunath Rao', with a stylized flourish at the end.

Manjunath Rao
Primary Patent Examiner 1652